

PROTOCOL

TITLE: A Long-Term Safety Study of Bruton's Tyrosine Kinase (Btk) Inhibitor PCI-32765 in B Cell Lymphoma and Chronic Lymphocytic Leukemia

PROTOCOL NUMBER: PCYC-1103-CA

STUDY DRUG: PCI-32765-00

IND NUMBER: 102688

SPONSOR MEDICAL MONITOR: Alvina Chu, MD
Pharmacyclics, Inc.
Phone: + 1 (408) 215-3027
Fax: +1 (408) 215-3684
Email: achu@pcyc.com

SPONSOR: Pharmacyclics, Incorporated
995 East Arques Avenue
Sunnyvale, CA 94085-4521

DATE FINAL:

Original:	02 April 2010
Amendment 1:	04 November 2011
Amendment 2:	19 June 2012
Amendment 3:	28 September 2012
Amendment 4:	16 January 2014
Amendment 5:	14 May 2015

CONFIDENTIALITY STATEMENT

This document is a confidential communication of Pharmacyclics provided to clinical investigators, study centers, associated individuals, and the like under the terms of existing confidentiality agreements. For example, this document may be disclosed to appropriate Investigational Review Boards under the condition that they maintain confidentiality consistent with their application procedures. Your acceptance and use of this document is subject to the condition that no information contained herein will be published or disclosed without first obtaining written approval from Pharmacyclics, Inc. If you do not agree to this condition, please return the document to Pharmacyclics at the above address.

PROTOCOL APPROVAL PAGE

I have carefully read Protocol PCYC-1103-CA entitled "A Long-Term Safety Study of Bruton's Tyrosine Kinase (Btk) Inhibitor PCI-32765 in B cell Lymphoma and Chronic Lymphocytic Leukemia," Amendment 5. I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board (IRB) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics, Inc. requires that any presentation or publication of study data by clinical investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature

Date

Print Name

The following Pharmacyclics, Inc. representative is authorized to sign the protocol and any amendments:

 MD
Alvina Chu, MD
Senior Medical Director
Pharmacyclics, Inc.

26 May 2015
Date

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITION OF TERMS6

STUDY SYNOPSIS8

1.0 BACKGROUND INFORMATION11

1.1 Investigational Product Name and Description11

1.2 Bruton’s Tyrosine Kinase and Lymphoma12

1.3 Summary of Relevant Nonclinical and Clinical Data12

1.3.1 Pharmacology12

1.3.2 Toxicology13

1.3.3 Pharmacokinetics and Product Metabolism14

1.4 Summary of Clinical Safety of PCI-3276515

1.4.1 Monotherapy Studies15

1.4.2 Combination Therapy Studies16

1.4.3 Risks16

1.5 Justification of Study Design and Dose Rationale18

1.6 Statement on Compliance19

2.0 STUDY OBJECTIVES AND PURPOSE19

3.0 STUDY DESIGN19

3.1 Description of Study19

3.2 Primary Endpoint20

3.3 Other Endpoints20

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS20

4.1 Inclusion Criteria20

4.2 Exclusion Criteria21

4.3 Discontinuation of Treatment21

4.4 Withdrawal from Study21

5.0 TREATMENT OF SUBJECTS22

5.1 Randomization and Blinding22

5.2 Formulation, Packaging, and Storage22

5.3 Dosage and Administration of PCI-3276522

5.4 Criteria for Adjusting Study Drug Dosage23

5.4.1 Dose Delay23

5.4.2 Dose Reduction and Discontinuation23

5.4.3 Intrasubject Escalation25

5.4.4 Dose Modification for Hepatic Impaired Subjects25

5.5 Concomitant Therapy25

5.5.1 Permitted Concomitant Therapy25

5.5.2	Prohibited Concomitant Therapy	25
5.6	Medications to be Used with Caution.....	26
5.6.1	CYP3A Inhibiting/Inducing Agents	26
5.6.2	Drugs That May Have Their Plasma Concentrations Altered by PCI-32765.....	26
5.6.3	Concomitant Use of QT Prolonging Agents.....	27
5.6.4	Concomitant Use of Antiplatelet Agents and Anticoagulants	27
5.6.5	Guidelines for PCI-32765 Management with Surgeries or Procedures.....	27
5.6.6	Reproductive Toxicity	28
5.6.7	Overdose Instructions	28
6.0	STUDY PROCEDURES	28
6.1	Description of Procedures.....	29
6.2	Investigator’s Assessment of Response to Treatment	32
6.2.1	Baseline Tumor Assessment.....	32
6.2.2	Assessment of Response to Treatment	32
6.3	Follow-up Phase.....	33
6.3.1	Safety Follow-up Visit.....	33
6.3.2	Post-treatment Phase.....	33
6.3.3	Post-disease Progression Phase.....	33
6.4	Missed Evaluations	33
7.0	ASSESSMENT OF SAFETY.....	34
7.1	Definitions ^{14,15}	34
7.1.1	Adverse Events	34
7.1.2	Serious Adverse Event.....	35
7.1.3	Severity	36
7.1.4	Causality	36
7.1.5	Unexpected Adverse Events	37
7.2	Documenting and Reporting of Adverse and Serious Adverse Events	37
7.2.1	Adverse Event Reporting Period	37
7.2.2	Assessment of Adverse Events	38
7.2.3	Expedited Reporting Requirements for Serious Adverse Events	38
7.2.4	Events of Special Interest.....	38
7.2.5	Pregnancy.....	39
7.2.6	Other Malignancies.....	39
7.2.7	Eye-Related Adverse Events.....	40
7.3	Reporting of Serious Adverse Events by Sponsor	40
8.0	STATISTICAL CONSIDERATIONS	40
9.0	STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS	40
9.1	Institutional Review Board and Independent Ethics Committee.....	41

9.2	Informed Consent.....	41
9.3	Protected Subject Health Information Authorization	42
9.4	Subject Screening Log	42
9.5	Source Documentation Requirements.....	42
9.6	Case Report Forms.....	42
9.7	Study Monitoring Requirements.....	43
9.8	Investigational Study Drug Accountability	44
9.9	Financial Disclosure.....	45
9.10	Availability and Record Retention.....	45
9.11	Protocol Amendments.....	46
9.12	Publication of Study Results.....	46
9.13	Liability and Clinical Study Insurance	47
10.0	REFERENCES.....	48
11.0	APPENDICES.....	50

IN-TEXT TABLES

Table 1:	Drug Discontinuation Actions for Subjects on PCI-32765.....	24
Table 2:	Intrasubject Dose De-escalation	24

LIST OF APPENDICES

Appendix 1.	Performance Status Scores.....	51
Appendix 2.	Inhibitors and Inducers of CYP 3A	52
Appendix 3.	Schedule of Assessments	53
Appendix 4.	Response Assessment Criteria for Chronic Lymphocytic Leukemia (Hallek) ⁹ ...	54
Appendix 5.	Response Assessment Criteria for Lymphoma (Cheson 2007) ¹⁰	56
Appendix 6.	Response Assessment Criteria for Waldenström's Macroglobulinemia (Kimby 2006) ¹¹	57
Appendix 7.	Child-Pugh Score ^{22,23}	58

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCR	B cell receptor
Btk	Bruton's tyrosine kinase
BUN	blood urea nitrogen
BW	body weight
CLL	chronic lymphocytic leukemia
CR	complete response
CRF	case report form
CRi	CR with incomplete blood count recovery
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B cell lymphoma
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
FDA	Food and Drug Administration
FDG	[¹⁸ F]fluorodeoxyglucose
GCP	Good Clinical Practice
HDPE	high-density polyethylene
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	informed consent form
IgH	immunoglobulin heavy chain
IRB	Institutional Review Board
MCL	mantle cell lymphoma
MedDRA [®]	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NHL	Non-Hodgkins lymphoma
PBMCs	peripheral blood mononuclear cells

Abbreviation	Definition
PCI-32765	oral formulation of PCI-32765 (study drug) provided in hard gelatin capsules also known as “PCI-32765 PO Hard Gelatin Capsule”
PD	progressive disease
PE	physical examination
PET	positron emission tomography
P-gp	permeability glycoprotein
PR	partial remission (response)
QTc	corrected QT interval
SAE	serious adverse event
SD	stable disease
SLL	small lymphocytic lymphoma
SOC	standard of care
SPD	sum of the product of the diameters
TLS	tumor lysis syndrome
ULN	upper limit of normal
WM	Waldenström's macroglobulinemia
XLA	X-linked agammaglobulinemia

STUDY SYNOPSIS

Title:	A Long-term Safety Study of Bruton’s Tyrosine Kinase (Btk) Inhibitor PCI-32765 in B Cell Lymphoma and Chronic Lymphocytic Leukemia
Protocol number:	PCYC-1103-CA
Phase:	Not applicable
Indication:	B cell lymphoma and chronic lymphocytic leukemia (CLL)
Study drug and comparator:	PCI-32765 PO Hard Gelatin Capsule (referred to as PCI-32765) No comparator is used in this study.
Objectives:	The primary objective is to determine the long-term (> 6 months) safety and tolerability of a fixed daily dosing regimen of PCI-32765.
Study design:	<p>This is an open-label, monotherapy, multicenter, extension study open to subjects meeting requirements for roll over from their parent protocol and want to continue receiving study drug. Subjects from PCYC-04753 who had disease progression may enroll in this study at a higher dose level of PCI-32765 (not to exceed 840 mg/day) than dose level in PCYC-04753 study.</p> <p>Subjects enrolled in this study will receive once daily dosing with PCI-32765 at the same dose level they were receiving in the parent study. One cycle is 28 days. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.</p> <p>Safety and efficacy assessments will be performed at a minimum of every 3 cycles. At each visit, adverse events (AEs) of Grade 3 or 4 in severity, which are either new or represent detectable exacerbations of pre-existing conditions, events of special interest and ongoing AEs from parent protocol will be recorded. All serious adverse events (SAEs) must be recorded. Efficacy assessments will be performed in accordance with the Guidelines for the Diagnosis and Treatment of CLL⁹ (Appendix 4), International Working Group Revised Response Criteria for Malignant Lymphoma¹⁰ (Appendix 5), and Waldenström's Macroglobulinemia (WM)¹¹ (Appendix 6). If signs and symptoms provide evidence of progressive disease (PD), PD must be confirmed by CT.</p> <p>Upon discontinuation of study treatment, a Safety Follow-up Visit (SFU) will be performed prior to the start of a new anticancer therapy or approximately 30 (±7) days after the last dose of study drug, whichever occurs first. If a subject discontinues treatment for reasons other than disease progression, response assessments will be continued approximately every 3 cycles until disease progression.</p> <p>Once a subject has progressive disease, collect subsequent anticancer therapy and subject survival status approximately once every 3 months. At a visit when it is determined that a subject has</p>

	<p>progressed, collect blood samples for pharmacodynamics and pharmacokinetics analyses (e.g., Btk occupancy and B cell activation) (refer to Section 6.1.)</p>
Major inclusion/exclusion criteria:	<p>For the complete list of inclusion/exclusion criteria refer to Section 4.0.</p> <p><u>Major Inclusion Criteria:</u></p> <ol style="list-style-type: none">1. Men and women with recurrent surface immunoglobulin positive B cell non-Hodgkin's lymphoma (NHL) according to WHO classification, (including, but not limited to, CLL/small lymphocytic lymphoma [SLL], Waldenström's macroglobulinemia [WM], mantle cell lymphoma [MCL], and diffuse large B cell lymphoma [DLBCL]) who have met requirements for roll over from their parent protocol and want to continue study drug.2. Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug and agree to use dual methods of contraception during the study and for 90 days following the last dose with study drug. Post menopausal females (>45 years old and without menses for >1 year) and surgically sterilized females are exempt from this criterion.3. Male subjects must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential.4. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.5. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations). <p><u>Major Exclusion Criteria:</u></p> <ol style="list-style-type: none">1. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of PCI-32765, or put the study outcomes at undue risk.2. Lactating or pregnant.
Endpoints:	<p>The primary endpoint of this study is the frequency, severity, and relatedness of AEs.</p> <p>Other endpoints of this study are:</p> <ul style="list-style-type: none">• Long-term tolerability as measured by treatment-related SAEs and discontinuation of study treatment due to AEs.• PD and death events• Documented responses

Safety plan:	This study will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and serious adverse events (SAEs) will be reviewed internally on an ongoing basis to identify safety concerns.
Study treatment:	PCI-32765 will be administered orally once daily at the same dose level of PCI-32765 as they received in the parent PCI-32765 study. Subject from PCYC-04753 who had disease progression may enroll in this study at a higher dose level of PCI-32765 (not to exceed 840 mg/day) than dose level in PCYC-04753 study. One cycle is 28 days.
Concomitant therapy and clinical practice:	<p>Concomitant medications which are permitted while on study treatment are provided in Section 5.5.1.</p> <p>Any chemotherapy (e.g., chlorambucil, bendamustine, cyclophosphamide, pentostatin, or fludarabine), anticancer immunotherapy (e.g., rituximab, alemtuzumab, or ofatumumab), experimental therapy, or radiotherapy are prohibited during the Treatment Phase. Localized, hormonal, or bone sparing treatment for non-B-cell malignancies may be considered with approval of the medical monitor. Localized radiotherapy for medical conditions other than the underlying B-cell malignancies are allowed after consultation and approval by the medical monitor. Corticosteroids at dosages equivalent to prednisone >20mg/day administered consecutively for 14 days or longer are prohibited. For medications to be used with caution refer to Section 5.6.</p>
Statistical methods:	<p>No formal statistical tests of hypotheses will be performed as this is an open-label, long-term, follow-up study. This study will remain open as long as there are active studies of PCI-32765 with subjects who could be eligible for this protocol.</p> <p>Demographic characteristics, laboratory parameters, concomitant therapy, and AE incidence rates will be summarized using descriptive statistics. All subjects who receive at least 1 dose of study drug will be included in the safety and efficacy analyses.</p> <p>All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Subjects lost to follow-up will be included in statistical analyses to the point of their last evaluation. All study data will be examined using standard data management operating procedures.</p>

1.0 BACKGROUND INFORMATION

Note: for more detailed and comprehensive background information please refer to the PCI-32765 Investigator's Brochure (IB).

1.1 INVESTIGATIONAL PRODUCT NAME AND DESCRIPTION

PCI-32765 (ibrutinib) is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, PCI-32765 inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. PCI-32765 (IMBRUVICA[®]; ibrutinib) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy, 2) chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy, 3) CLL in patients with 17p deletion, and 4) Waldenström's Macroglobulinemia. PCI-32765 is currently under investigation in various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways.¹⁸

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development.¹⁹ Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B cells. The BTK protein is expressed in most hematopoietic cells with the exception of T cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B cells.¹

Data from Study PCYC-04753 demonstrate that although PCI-32765 is rapidly eliminated from the plasma after oral administration, once daily dosing with PCI-32765 is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥ 2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

For the most comprehensive nonclinical and clinical information regarding PCI-32765 background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of PCI-32765, refer to the latest version of the PCI-32765 IB.

1.2 BRUTON'S TYROSINE KINASE AND LYMPHOMA

Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B cell malignancies. First, expression of a functional BCR is maintained throughout lymphoma progression even as the non-expressed immunoglobulin heavy chain (IgH) is involved in oncogenic translocations and despite prolonged treatment of tumor cells with anti-idiotype therapies.^{2,3} In addition, selective knockdown of BCR components by RNA interference results in apoptosis in multiple B cell lymphoma cell lines.⁴

Recent studies indicate that some large-cell lymphomas have low-level tonic activation of the kinases downstream of the BCR and that inhibition of this tonic signaling can induce apoptosis.⁵ Primary follicular lymphoma cells have also been found to maintain enhanced signaling from the BCR compared with normal B cells.⁶ In addition, at least 2 drugs that target BCR signaling (the Syk inhibitor, R788, and the PKC β inhibitor, enzastaurin) have shown evidence of anti-tumor effects in human B cell lymphomas.⁷

1.3 SUMMARY OF RELEVANT NONCLINICAL AND CLINICAL DATA

1.3.1 Pharmacology

PCI-32765 was designed as a selective and covalently-binding inhibitor of the Btk protein.⁸ In vitro, PCI-32765 is a potent inhibitor of Btk activity ($IC_{50} = 0.39$ nM). The irreversible binding of PCI-32765 to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, PCI-32765 inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation ($IC_{50} = 80$ nM) as assayed by anti-IgM stimulation followed by CD69 expression.²⁰

PCI-32765 arrested cell growth and induced apoptosis in human B cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models. In mice, tumor growth inhibition was demonstrated at dose levels where no overt toxicity was observed, as measured by body weights (BWs). In addition, PCI-32765 was efficacious in a mouse model of collagen-induced arthritis, a disease whose pathogenesis involves B cell activation.

Binding of PCI-32765 to the active site of Btk (Btk occupancy) was demonstrated in vivo in rat and dog blood mononuclear cells, mouse splenocytes, and xenograft tumor cells using a pharmacodynamic assay, which uses a specially designed Btk-binding fluorescent probe. The probe binds irreversibly to the active site of Btk, enabling fluorescent detection of labeled Btk protein. The presence of PCI-32765 bound to the Btk active site occludes probe binding thus reducing the fluorescence probe signal. In mice, 50% of the Btk active sites in splenocytes were occupied 3 hours after a single oral dose of PCI-32765 at 5 mg/kg. Mice orally administered PCI-32765 30 mg/kg had complete Btk active-site occupancy in splenocytes, which persisted about 12 hours post dose. In dogs, a single oral dose of 10 mg/kg resulted in complete occupancy of Btk measured in PBMCs. The complete occupancy persisted for ≥ 24 hours with partial recovery by 48 hours post dose. PCI-32765 added to human blood (ex vivo) leads to complete Btk occupancy ($IC_{50} = 100$ nM) and inhibition of B cell activation measured by CD69 expression.

1.3.2 Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with PCI-32765 is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that PCI-32765 is not genotoxic. In a rat embryo-fetal toxicity study PCI-32765 administration was associated with fetal loss and malformations (teratogenicity) at PCI-32765 doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively.

1.3.2.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with PCI-32765.

PCI-32765 was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with PCI-32765 have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered PCI-32765 did not result in adverse effects on reproductive organs.

1.3.3 Pharmacokinetics and Product Metabolism

Following oral administration of PCI-32765 at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to PCI-32765 increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of PCI-32765 across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg PCI-32765 with a high-fat breakfast in subjects with chronic lymphocytic leukemia (CLL) approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. PCI-32765 was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of Btk, with approximately 15 times lower inhibitory potency compared to PCI-32765. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of PCI-32765 and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [14 C]-PCI-32765 conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [14 C]-PCI-32765 is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance >30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. In a hepatic impairment study, data showed an increase in PCI-3276 exposure. Following single dose administration, the AUC of PCI-32765 increased 2.7-, 8.2-, and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of PCI-32765 has not been evaluated in patients with hepatic impairment.

1.4 SUMMARY OF CLINICAL SAFETY OF PCI-32765

For a comprehensive summary of nonclinical and clinical information regarding the efficacy and safety of PCI-32765, refer to the current version of the IB.

1.4.1 Monotherapy Studies

Pooled safety data for subjects treated with PCI-32765 monotherapy in 11 nonrandomized studies (PCYC-1102-CA, PCYC-1117-CA, PCYC-1112-CA [crossover only], PCYC-1104-CA, PCI-32765MCL2001, PCI-32765MCL4001, PCYC-1106-CA, PCYC-1111-CA, PCI-32765FLR2002, PCYC-04753, and PCI-32765-JPN-101) has been evaluated.

The most frequently reported treatment-emergent adverse events (AEs) in more than 10% of subjects receiving PCI-32765 as monotherapy in nonrandomized studies (N=1061) were diarrhea (35.9%), fatigue (28.6%), nausea (20.2%), cough (17.5%), and anemia (15.2%). The most commonly reported Grade 3 or 4 AEs that were hematologic in nature were neutropenia (10.7%), thrombocytopenia (6.2%), and anemia (5.5%). Pneumonia (5.7%), fatigue (2.9%), hypertension (2.7%), and atrial fibrillation (2.6%) were the most frequently reported nonhematologic Grade 3 or 4 AEs.

The incidence of treatment-emergent SAEs reported was 41.3%. (N=1061); pneumonia (7.0%), atrial fibrillation (2.8%), and febrile neutropenia (2.3%) were the most commonly reported treatment-emergent SAEs.

In a randomized Phase 3 study in subjects with CLL/SLL (PCYC-1112-CA) the most frequently reported treatment-emergent AEs in the PCI-32765 arm were diarrhea (47.7%), fatigue (27.7%), nausea (26.2%), pyrexia (23.6%), anemia (22.6%), and neutropenia (21.5%). Adverse events reported at a higher incidence (>10% difference) in the PCI-32765 arm than in the ofatumumab arm included diarrhea (PCI-32765: 47.7%, ofatumumab: 17.8%), arthralgia (17.4%, 6.8%), and petechiae (13.8%, 1.0%).

The most commonly reported Grade 3 or 4 AEs in more than 2% of PCI-32765 treated subjects that were hematologic in nature were neutropenia (16.4%), thrombocytopenia (5.6%), and anemia (4.6%). Pneumonia (6.7%) was the most frequently reported nonhematologic event. The most frequently reported SAEs in PCI-32765 subjects were pneumonia (8.7%), atrial fibrillation (3.1%), pyrexia (3.1%), lung infection (2.6%), lower respiratory tract infection (2.1%) and urinary tract infection (2.1%). For more detailed information please refer to the current version of the IB.

1.4.2 Combination Therapy Studies

Pooled safety data for subjects (N=136) treated with PCI-32765 as combination therapy in 3 non-randomized studies (PCI-32765 + BR or FCR (n=33); PCI-32765 + ofatumumab (n=71), and PCI-32765 + R-CHOP (n=32) are summarized below. The median duration of treatment was 11.1 months (range: 0.0 to 19.5).

The most frequently reported treatment-emergent AEs reported in more than 10% of subjects were diarrhea (62.5%), nausea (45.6%), neutropenia (37.5%), fatigue (32.4%), peripheral sensory neuropathy (30.9%), upper respiratory tract infection (26.5%), vomiting (26.5%), anemia (21.3%), and thrombocytopenia (21.3%). The most commonly reported Grade 3 or 4 AEs were: neutropenia (36.0%), pneumonia (8.1%), febrile neutropenia (7.4%), thrombocytopenia (7.4%), diarrhea (5.1%), anemia (4.4%), cellulitis (4.4%) and urinary tract infection (4.4%).

Treatment-emergent SAEs in subjects receiving PCI-32765 as combination therapy (N=136) were reported in 39.0% of subjects. The most frequently reported serious AEs were pneumonia (8.8%), febrile neutropenia (7.4%), cellulitis (4.4%), and atrial fibrillation (2.9%).

For more detailed information please refer to the current version of the IB.

1.4.3 Risks

1.4.3.1 Lymphocytosis and Leukostasis

Similar to other agents targeting BCR signaling, transient lymphocytosis is a pharmacodynamic effect of PCI-32765, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood.²¹

A reversible increase in lymphocyte counts (ie, $\geq 50\%$ increase from baseline and above absolute count 5,000/ μL), often associated with reduction of lymphadenopathy has been observed in most subjects (approximately 69% to 75%) with CLL/SLL treated with single agent PCI-32765. This effect has also been observed in some subjects (33%) with MCL treated with single agent PCI-32765. This observed transient lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks (median time 1.1 weeks) of PCI-32765 therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving PCI-32765 in combination with chemoimmunotherapy (ie, 27% of subjects receiving ibrutinib + bendamustine + rituximab (BR) in Study 1108) or immunotherapy (ie, 55% of subjects receiving ibrutinib + ofatumumab in Group 2 of Study 1109).

A substantial increase in the number of circulating lymphocytes (eg, >400,000/ μ L) has been observed in a subset of subjects. There have been isolated cases of leukostasis reported in subjects treated with PCI-32765.

1.4.3.2 Bleeding-related Events

Major bleeding events including fatal events have occurred in subjects treated with PCI-32765, both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events including gastrointestinal bleeding, post procedural hemorrhage, intracranial hemorrhage, and hematuria.

1.4.3.3 Rash

Rash has been commonly reported in subjects treated with either single agent PCI-32765 or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the PCI-32765 arm than in the control arm. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a subject with CLL. The subject received PCI-32765 (420 mg/day) and was also receiving various antibiotics and antigout medication (allopurinol) known to be associated with SJS.

1.4.3.4 Other Malignancies

Other malignancies, most frequently skin cancers, have occurred in subjects treated with PCI-32765. Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with PCI-32765. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

1.4.3.5 Cardiac

Atrial fibrillation and atrial flutter have been reported in subjects treated with PCI-32765, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. In particular subjects with a history of cardiac arrhythmias should be monitored closely.

1.4.3.6 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with PCI-32765.

1.4.3.7 Diarrhea

Approximately one-third of subjects treated with PCI-32765 monotherapy and two-thirds treated with combination therapy reported diarrhea. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe, with only a small number of Grade 3 events, and no Grade 4 events reported to date.

1.4.3.8 Infections

Fatal and non-fatal infections have occurred with PCI-32765 therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with PCI-32765.

1.4.3.9 Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent PCI-32765 or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated LDH, bulky disease at baseline, and pre-existing kidney abnormalities.

1.5 JUSTIFICATION OF STUDY DESIGN AND DOSE RATIONALE

This study is a long-term safety and efficacy extension study. It allows subjects meeting requirements for roll over from their parent protocol and who want to continue receiving study drug to continue on study drug. This reduces the burden of study visits and tests on the subjects and allows them to continue to have access to the investigational product.

The starting dose level for all subjects enrolled in this study will be based on the dose level the subject was receiving in the parent study. Study drug will be administered continuously without interruption. If the subject was in a weight-based dose cohort (subjects from PCYC-04753

study), then the fixed dose up to 840 mg/day that most closely approximates the weight-based dose will be chosen (refer to [Section 5.4.2](#) for information on dose adjustments).

1.6 STATEMENT ON COMPLIANCE

This study will be conducted in compliance with this protocol, principles of International Conference on Harmonisation (ICH) GCP, Declaration of Helsinki, and all applicable national and local regulations governing clinical studies.

2.0 STUDY OBJECTIVES AND PURPOSE

The purpose of this study is to determine the long-term safety of a fixed-dose, daily regimen of PCI-32765 at dose levels up to 840 mg/day in subjects with B cell lymphoma (including, but not limited to, CLL/SLL, Waldenström's macroglobulinemia [WM], mantle cell lymphoma [MCL], diffuse large B cell lymphoma [DLBCL], and follicular lymphoma [FL]).

The primary objective is to determine the long-term (>6 months) safety and tolerability of a fixed daily dosing regimen of PCI-32765.

3.0 STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is an open-label, monotherapy, multicenter, extension study open to subjects from prior PCI-32765 studies who meet eligibility criteria. This is an open-label study; as such, no blinding measures will be taken.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase.

The Screening Phase will be the last Treatment Phase of the parent protocol. Subjects will complete all safety and efficacy assessments required by the parent protocol, and roll over to this extension study to ensure no interruption of treatment with PCI-32765.

The Treatment Phase will extend from the first dose until study drug discontinuation under this protocol. Subjects roll over from PCI-32765 and chemotherapy combination studies will receive PCI-32765 only in this study. Subjects will receive PCI-32765 once-daily dosing at the dose level the subject was receiving in the parent study until disease progression. Please note that if the clinical risk benefit ratio favors continuing PCI-32765 for a brief period of time (e.g. up to 4 weeks) while salvage anticancer therapy is arranged that this may be considered at the Investigators discretion. Regularly scheduled safety and efficacy assessments are required throughout the Treatment Phase. Further information on dosing is provided in [Section 5.3](#).

The Follow-up Phase will comprise of 2 phases; a Post-treatment Phase and a Post-disease Progression Phase. The Post-treatment Phase will extend from the discontinuation of treatment up until the subject has PD or other criteria listed in [Section 4.3](#). A Safety Follow-Up Visit (SFU) will be performed prior to the start of a new anticancer therapy or 30 (\pm 7) days after the last dose of study drug, whichever occurs first. If a subject discontinues treatment for reasons other than disease progression, response assessments will be continued every 3 cycles until disease progression.

The Post-disease Progression Phase will begin once a subject has progressive disease. In this phase, collection of subsequent anticancer therapy and subject survival status should be performed once every 3 months.

This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. This study will remain open as long as there are active studies of PCI-32765 with subjects who may be eligible for this protocol.

3.2 PRIMARY ENDPOINT

The primary endpoint of this study is the frequency, severity, and relatedness of AEs.

3.3 OTHER ENDPOINTS

Other endpoints of this study are:

- Long-term tolerability as measured by treatment-related SAEs and discontinuation of study treatment due to AEs
- PD and death events
- Documented responses

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 INCLUSION CRITERIA

Eligible subjects will be considered for inclusion in this study if they meet all of the following criteria:

1. Men and women with recurrent surface immunoglobulin positive B cell non-Hodgkin's lymphoma (NHL) according to WHO classification (including, but not limited to, CLL/SLL, Waldenström's macroglobulinemia [WM], mantle cell lymphoma [MCL], and diffuse large B cell lymphoma [DLBCL]) who have met requirements for roll over from their parent protocol and want to continue study drug.

2. Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug and agree to use dual methods of contraception during the study and for 90 days following the last dose with study drug. Post menopausal females (>45 years old and without menses for >1 year) and surgically sterilized females are exempt from this criterion.
3. Male subjects must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential.
4. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
5. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

4.2 EXCLUSION CRITERIA

Subjects will be ineligible for this study if they meet any 1 of the following criteria:

1. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of oral PCI-32765, or put the study outcomes at undue risk.
2. Lactating or pregnant.

4.3 DISCONTINUATION OF TREATMENT

If the subject meets any of the following criteria, subject may be discontinued from study treatment:

- Progressive disease as determined by histology-specific criteria (refer to [Appendix 4](#), [Appendix 5](#), and [Appendix 6](#))
- Adverse event
- Death
- Withdrawal from treatment by subject
- Investigator decision
- Lost to follow-up
- Study terminated by Sponsor

No subject will be replaced. Ongoing AEs (see [Section 7.0](#)) at time of discontinuation will be followed until 30 days after the last dose of PCI-32765.

4.4 WITHDRAWAL FROM STUDY

A subject may be withdrawn from the study for any of the following reasons including:

- Death

- Lost to follow-up
- Study terminated by Sponsor
- Withdrawal of consent

In case a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. The measures taken to follow-up must be documented in the subject's records.

When a subject withdraws before study closure, the reason for withdrawal must be documented in the source documents.

5.0 TREATMENT OF SUBJECTS

5.1 RANDOMIZATION AND BLINDING

Subjects enrolled will receive open-label PCI-32765 only. No randomization or blinding of study drug administration will occur during this study.

5.2 FORMULATION, PACKAGING, AND STORAGE

PCI-32765 is provided as a size 0 hard gelatin capsule containing 140 mg of PCI-32765. The capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. The drug product is manufactured for Pharmacyclics, Inc. by a contract manufacturer. All formulation excipients are compendial and are commonly used in oral formulations.

The recommended storage condition for PCI-32765 is room temperature. If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Worksheet should be completed and faxed to Pharmacyclics or designee. Refer to the IB for additional information regarding the drug product to be used in this study.

5.3 DOSAGE AND ADMINISTRATION OF PCI-32765

Subjects will receive daily administration of a fixed dose of PCI-32765. Subjects will continue treatment at the same dose level as in the parent study (up to 840 mg) daily. Subjects whose dose level was previously determined on the basis of weight (PCYC-04753) will receive a fixed dose of PCI-32765 (not to exceed 840 mg/day) that is comparable to their prior weight-based dose level. PCI-32765 is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water. Avoid grapefruit juice or Seville oranges due to CYP3A inhibition. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

Each dose of PCI-32765 should be taken at approximately the same time each day. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

At any given visit, only enough PCI-32765 to last until the next visit should be dispensed. Unused PCI-32765 capsules dispensed during previous visits and all empty bottles should be returned and drug accountability records ([Section 9.8](#)) updated according to the schedule in [Appendix 3](#). Returned capsules must not be redispensed to the same subject or to another subject. Empty bottles should be destroyed at the site or returned to the Sponsor.

A subject diary will be used to aid with study drug administration compliance. Investigators are prohibited from supplying PCI-32765 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as sub-investigators on form Food and Drug Administration (FDA) 1572. The investigator must ensure that subjects receive PCI-32765 only from personnel who fully understand the procedures for administering the drug.

5.4 CRITERIA FOR ADJUSTING STUDY DRUG DOSAGE

5.4.1 Dose Delay

Treatment with PCI-32765 should be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity. Subjects who require anticoagulant treatment (e.g., heparin and/or warfarin) should have study drug held until stabilized on anticoagulant therapy.

Study drug may be held for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the medical monitor.

5.4.2 Dose Reduction and Discontinuation

At the discretion of the investigator, based upon the recent FDA approvals of IMBRUVICA[®] (PCI-32765) for the treatment of MCL and CLL after having received at least one prior therapy and for the treatment of WM, subjects may have their PCI-32765 dose reduced to the approved dosage in the absence of toxicity. Any subsequent dose modifications below the approved label dose should follow the dose modification guidelines per protocol for toxicity.

The actions in [Table 1](#) should be taken for the following toxicities:

- Grade 4 ANC (< 500/ μ L) for > 7 days (neutrophil growth factors are permitted per ASCO guidelines¹⁶ and use must be recorded in CRF).

- Grade 3 thrombocytopenia (< 50,000/ μ L) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (< 25,000/ μ L).
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- Any other Grade 4 toxicity or any unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of PCI-32765 treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 5.6.4).

Table 1: Drug Discontinuation Actions for Subjects on PCI-32765

Occurrence	Action
1 st	Hold PCI-32765 until recovery to Grade \leq 1 or baseline; may restart at original dose level
2 nd	Hold PCI-32765 until recovery to Grade \leq 1 or baseline; restart at one dose level lower (140mg less daily)*
3 rd	Hold PCI-32765 until recovery to Grade \leq 1 or baseline; restart at one dose level lower (140mg less daily)*
4 th	Discontinue PCI-32765

* Reference Table 2 for details on dose de-escalation of 420, 560 and 840 mg dose group.

Changes must be recorded in the Dose Administration eCRF and subject’s records.

A high number of circulating malignant cells (>400000/mcL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukopheresis as indicated. PCI-32765 may be temporarily held, and medical monitor should be contacted.

Table 2: Intrasubject Dose De-escalation

Assigned Daily Dose	420 mg (3 x 140-mg)	560 mg (4 x 140-mg)	840 mg (6 x 140-mg)
Dose De-escalation Level 1	280 mg (2 x 140-mg)	420 mg (3 x 140-mg)	700 mg (5 x 140-mg)
Dose De-escalation Level 2	140 mg (1 x 140-mg)	280 mg (2 x 140-mg)	560 mg (4 x 140-mg)

5.4.3 Intrasubject Escalation

At the Investigator's discretion, the dose of study drug may be re-escalated after 2 cycles following a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

5.4.4 Dose Modification for Hepatic Impaired Subjects

PCI-32765 is metabolized in the liver. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for PCI-32765 is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better and could be re-treated according to resolved hepatic conditions (ie, 140 mg or 280 mg for moderate or mild impairment, respectively). Monitor subjects for signs of toxicity and follow dose modification guidance as needed [Appendix 7](#).

5.5 CONCOMITANT THERAPY

5.5.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per the American Society of Clinical Oncology (ASCO) guidelines¹⁶. Transfusions may be given in accordance with institutional policy.

Short courses (≤ 14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

Treatment for autoimmune cytopenias is permitted for < 14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

5.5.2 Prohibited Concomitant Therapy

Any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited during the Treatment Phase. Localized, hormonal, or bone sparing treatment for non-B-cell malignancies may be considered with approval of the medical monitor.

Localized radiotherapy for medical conditions other than the underlying B-cell malignancies are allowed after consultation and approval by the medical monitor.

5.6 MEDICATIONS TO BE USED WITH CAUTION

5.6.1 CYP3A Inhibiting/Inducing Agents

PCI-32765 is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and AUC_{0-last} , of PCI-32765 by 29- and 24-fold, respectively. The maximal observed PCI-32765 exposure (AUC) was ≤ 2 -fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the highest PCI-32765 exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, reduce the PCI-32765 dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of PCI-32765 toxicity. If a moderate CYP3A inhibitor must be used, reduce PCI-32765 to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Avoid grapefruit and Seville oranges during PCI-32765 treatment, as these contain moderate inhibitors of CYP3A (see [Section 5.3](#)).

Co-administration of PCI-32765 with a strong CYP3A inducer, rifampin, in healthy subjects decreases PCI-32765 plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort).

Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in [Appendix 2](#); a comprehensive list of inhibitors, inducers, and substrates may be found at <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. This website is continually revised and should be checked frequently for updates.

5.6.2 Drugs That May Have Their Plasma Concentrations Altered by PCI-32765

In vitro studies indicated that PCI-32765 is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 $\mu\text{g/mL}$). PCI-32765 is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that PCI-32765 could inhibit

intestinal P-gp after a therapeutic dose. There are no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after PCI-32765.

5.6.3 Concomitant Use of QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic electrocardiogram (ECG) and electrolyte monitoring should be considered.

5.6.4 Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with PCI-32765. Supplements such as fish oil and vitamin E preparations should be avoided. Use PCI-32765 with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on PCI-32765 and the use of anticoagulants during procedures/surgeries see [Section 5.6.5](#).

Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing PCI-32765 treatment. If therapeutic anticoagulation is clinically indicated, treatment with PCI-32765 should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. No dose reduction is required when study drug is restarted.

5.6.5 Guidelines for PCI-32765 Management with Surgeries or Procedures

PCI-32765 may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of PCI-32765 in the peri-operative period for subjects who require surgical intervention or an invasive procedure while receiving PCI-32765.

5.6.5.1 Minor Procedures

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) PCI-32765 should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on PCI-32765, it is not necessary to hold PCI-32765 for these procedures.

5.6.5.2 Major Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, PCI-32765 should be held at least 7 days prior to the intervention and should be held at least 7 days after the

procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

5.6.5.3 Emergency Procedures

For emergency procedures (unscheduled/urgent), PCI-32765 should be held for a minimum of 7 days after the urgent surgical procedure and until the surgical site is reasonably healed.

5.6.6 Reproductive Toxicity

Reproductive toxicity studies have not been done with PCI-32765. Therefore, women of child-bearing potential who are sexually active must use highly effective contraception during the study and for 90 days after the last dose of PCI-32765. Men who are sexually active, must use highly effective contraception during the study and for 90 days (3 months) after the last dose of PCI-32765. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue PCI-32765 immediately. Pregnancy in a female subject or a male subject's partner must be reported in the same manner as a SAE (refer to [Section 7.2.3](#)).

5.6.7 Overdose Instructions

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as an SAE in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific antidote for ibrutinib. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

6.0 STUDY PROCEDURES

The Schedule of Assessments is shown in [Appendix 3](#). Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in [Section 5.0](#).

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. All results from these evaluations must be captured in the provided electronic case report forms (eCRFs).

6.1 DESCRIPTION OF PROCEDURES

Informed Consent

Screening

The subject must read, understand and sign the IRB-approved informed consent form (ICF) confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information.

Medical History

Screening

Medical history, concomitant medications, and any ongoing signs or symptoms from the prior PCI-32765 protocol must be recorded in the site's source documentation.

Adverse Events

At all visits (except Post-treatment and Post-PD follow up assessments)

The accepted regulatory definition for an AE is provided in [Section 7.1](#). Adverse events that meet the criteria for SAEs, events of special interest ([Section 7.2.4](#)), and AEs of grade 3 or higher in severity will be recorded from the subject's first dose of study drug until 30 days after study drug discontinuation or start of a new anticancer therapy. Important additional requirements for reporting SAEs are explained in [Section 7.2](#).

Concomitant Medication Use

At screening visit and during study when associated with protocol specified AE or SAE.

Verify concomitant medication use to ensure subjects' eligibility to remain on study and when associated with a protocol specified AE/SAE. See [Section 7.0](#) for further AE/SAE details.

Confirmation of Eligibility

Screening

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion. Screening evaluations must be completed within 14 days before the subject's first dose of PCI-32765 under this protocol.

Physical Examination and Vital Signs

At all visits (except Post treatment and Post PD follow up assessments)

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period and at the Safety Follow-up Visit.

Vital signs will include blood pressure, pulse, respiratory rate, and body temperature. Vital signs and weight will be measured at every visit. Screening vital signs and weight do not need to be repeated if performed on prior PCI-32765 protocol within 14 days before the first administration of study drug on this protocol.

Eye-related Symptom Assessment

At Screening and all physical exams while on Treatment and Safety Follow-up.

The subjects will be asked about eye-related symptoms at Screening and with all subsequent physical exams while on treatment.

If there are any eye-related symptoms of severity Grade ≥ 2 at Screening or if the subject develops any eye-related symptoms of severity Grade ≥ 2 while on study treatment, an ophthalmologic evaluation/consult must be performed and the outcome must be reported on the ophthalmologic eCRF.

ECOG Performance Status

Treatment Phase and Safety Follow-up Visit

The ECOG performance index is provided in [Appendix 1](#).

Hematology

Screening, Treatment Phase and Safety Follow-up Visit

Hematology must include complete blood count with differential and platelet counts. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. Screening hematology does not need to be repeated if performed on prior PCI-32765 protocol within 14 days before the first administration of study drug on this protocol. Subjects who roll into PCYC-1103-CA Study with < 12 months of study drug exposure will need to have hematology performed every 30 days (± 7 days) until completion of 12 months on study drug and then hematology will be extended to every 3 months (± 7 days).

Serum Chemistry

Screening, Treatment Phase and Safety Follow-up Visit

Serum chemistry must include glucose, calcium, albumin, total protein, sodium, potassium, CO₂, chloride, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, ALT, AST, and total bilirubin. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. Screening chemistry does not need to be repeated if performed on prior PCI-32765 protocol within 14 days before the first administration of study drug on this protocol.

Urine Pregnancy Test

Screening and Safety Follow-up Visit

Pregnancy tests are required only for women with childbearing potential. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

ECG

Treatment Phase and Safety Follow-up Visit

ECGs should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea.

Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. During visits in which both ECGs and blood draws are performed, ECGs should be performed first.

Pharmacodynamics and Pharmacokinetics

Only when subject progresses

At a visit when it is determined that a subject has progressed, collect blood samples for pharmacodynamic and pharmacokinetics analyses (e.g., Btk occupancy and B cell activation).

- Pharmacodynamic sample should be collected 4 hours post last dose of PCI-32765.
- Pharmacokinetic samples should be collected pre-dose and 4 hours post last dose of PCI-32765.

If Pharmacodynamic and Pharmacokinetic samples cannot be collected at specified timepoints, draw a random sample and capture time of collection and time of last PCI-32765 dose.

Refer to the laboratory binder for instructions on collecting and processing these samples.

If available, tumor samples should also be collected at the visit when disease progression is determined.

Predictive Biomarkers and Mechanisms of Treatment Resistance

Treatment Phase

Blood samples will be collected and assessed or maintained centrally to evaluate potential biomarkers related to response to therapy and/or to investigate potential mechanisms of treatment resistance. These samples may be later characterized by technologies such as gene expression profiling, mutational analysis by sequencing, or proteomic assays. Inhibition of BTK and other related kinases may also be explored in these cells. It is expected that these efforts may identify genes and pathways associated with primary or later development of resistance to PCI-32765 by comparison of subjects with variable outcomes which could potentially generate biomarkers that could assist with future development of this compound.

Disease Assessment

Treatment Phase and Post-treatment Follow-up Phase

Disease assessments, as outlined by histology-specific guidelines, should be performed every 3 cycles (± 7 days) while on study treatment. Disease assessments will include physical examination, disease-related symptoms, CBC, radiologic exam by computed tomography (CT) scan or positron emission tomography (PET), and/or bone marrow biopsy (refer to [Section 6.2](#) for response assessment guidelines). Data from bone marrow examinations, including analysis for minimal residual disease (MRD) (bone marrow or peripheral blood if bone marrow is unavailable or considered inappropriate), will be collected and should be performed if subject meets all other criteria for CR.

Study Drug Accountability

At all visits (except Follow-up Phase)

Refer to [Section 9.8](#).

6.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

The investigator must evaluate the subject's response to treatment based on Guidelines for the Diagnosis and Treatment of CLL⁹ ([Appendix 4](#)), International Working Group Revised Response Criteria for Malignant Lymphoma¹⁰ ([Appendix 5](#)), and Waldenström's Macroglobulinemia (WM)¹¹ ([Appendix 6](#)).

6.2.1 Baseline Tumor Assessment

As this is a long-term extension study, the baseline tumor assessments are derived from the baseline tumor assessment from the prior PCI-32765 protocol.

The exception is those subjects from PCYC-04753 who had disease progression and enrolled in this study to receive higher dose level. Their baseline tumor assessment must be done within 30 days of starting on this protocol.

6.2.2 Assessment of Response to Treatment

Objective response will be categorized as complete response (CR), complete response with incomplete marrow recovery (CRi), nodular partial response (nPR), partial response (PR), partial response with lymphocytosis (PRL), stable disease (SD), or progressive disease (PD) based on the guidelines of each histology (refer to [Appendix 4](#), [Appendix 5](#), and [Appendix 6](#)). The response assessments will be performed once every 3 cycles (± 7 days) during the Treatment Phase. All responses must be maintained for at least 2 months to be considered confirmed. To facilitate lymph node, liver, and spleen assessments in subjects, obtain a CT scan of the chest,

abdomen, and pelvis, every 3 cycles for the first 18 cycles from the subject's first dose of study drug in the parent study, then every 6 cycles up to cycle 36, then every 12 cycles (annually) thereafter.

- Progressive Disease (PDs) must be confirmed by CT scan.
- Complete responses (CRs) must be confirmed by bone marrow biopsy/aspirate. For subjects who obtain complete response (CR), subsequent scans are only required to confirm disease progression.

6.3 FOLLOW-UP PHASE

After study Treatment Phase is completed, all subjects will enter the Follow-up Phase. The Follow-up Phase will comprise of the following:

- Safety Follow-up Visit
- Post-treatment Phase
- Post-disease Progression Phase

6.3.1 Safety Follow-up Visit

The Safety Follow-up Visit will be conducted prior to the start of a new anticancer treatment or 30 (± 7) days after the last PCI-32765 dose, whichever occurs first, to monitor for ongoing AEs (refer to [Section 7.0](#)) and to document the occurrence of any new AEs. The Schedule of Assessments ([Appendix 3](#)) describes the procedures required for the Safety Follow-up Visits.

6.3.2 Post-treatment Phase

The Post-treatment Phase will extend from the discontinuation of treatment up until the subject has progressive disease or other criteria listed in [Section 4.3](#). Subjects will be followed approximately every 3 months (± 7 days) for disease progression and initiation of any subsequent anticancer therapy.

6.3.3 Post-disease Progression Phase

After disease progression, follow subject for survival status (including cause of death) by clinic visit or phone contact, as well as collection of subsequent anticancer therapy once every 3 months (± 7 days) until the end of study.

6.4 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion,

medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

7.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording Grade 3 or 4 AEs, SAEs, AEs of special interest ([Section 7.2.4](#)) and measurements of protocol-specified physical exam; and other tests to ensure patient safety.

7.1 DEFINITIONS^{14,15}

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug.

For the purposes of this clinical study, AEs include only grade 3 or 4 events which are either new or represent detectable exacerbations of pre-existing conditions or events of special interest (see protocol [Section 7.2.4](#)).

The following are exceptions that will be collected as AE's regardless of severity grade:

- AE leading to dose reduction
- AE leading to treatment discontinuation
- SAE
- Other malignancies
- Eye-related adverse events Grade 2 or higher

Disease progression is not an adverse event; rather it may be the cause of an adverse event.

Adverse events that occur due to disease progression must be reported as all other treatment-emergent adverse events. "Disease progression" should never be an adverse event term.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through 30 days after last dose of study drug.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period (refer to [Section 7.2.1](#)).

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered an AE:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history case report form [CRF]) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration but not performed before enrollment in the study will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Asymptomatic Treatment-Related Lymphocytosis:** This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

7.1.2 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). “Serious” is a regulatory definition.

An SAE (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death (i.e., the AE actually causes or leads to death)
- is life-threatening (“life-threatening” is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.)
- requires inpatient hospitalization >24 hours or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject’s ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient, or patient may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the investigator believes that the event is serious, the event will be considered serious.

7.1.3 Severity

Definitions found in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities.
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment.
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death.
- Grade 5 (Death related to AE) – experiences which result in subject death.

7.1.4 Causality

The investigator is to assess the causal relation (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Unrelated: Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Definitely Related: The AE is clearly related to use of the investigational product.

7.1.5 Unexpected Adverse Events

An “unexpected” AE is an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

7.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRFs. All SAEs also must be reported on the SAE Worksheet.

7.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject takes the first dose of study drug and ends 30 days after the last dose of study drug. Ongoing AEs from parent protocol must be followed to resolution or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. SAEs occurring after 30 days following the last dose of study drug should also be reported if considered related to study drug. If an SAE is present at the Safety Follow-up Visit, the SAE (and associated AEs and concomitant medications) should be followed to resolution or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

If a death occurs within 30 days after the last dose of study drug the death must be reported to the Sponsor as an SAE.

7.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on a SAE Worksheet.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the investigational product (see following guidance), and any actions taken.

7.2.3 Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on a SAE Worksheet and faxed to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes, laboratory results).

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Pharmacyclics Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

7.2.4 Events of Special Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the Sponsor within 24 hours of awareness following the procedure described above for SAEs ([Section 7.2.3](#)) and will require enhanced data collection. **All Events of Special Interest will be submitted without a serious criterion selected if no other serious criterion is met.**

7.2.4.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher.^a
- Any treatment-emergent serious adverse events of bleeding of any grade

- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade
 - a. All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to [Section 7.2.4](#) above.

7.2.5 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the investigator if the subject becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the investigator if the subject's partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving PCI-32765 who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. The pregnant female will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a SAE.

7.2.6 Other Malignancies

In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

7.2.7 Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline worsens, should be evaluated by an ophthalmologist whose findings should be reported on the ophthalmologic eCRF.

7.3 REPORTING OF SERIOUS ADVERSE EVENTS BY SPONSOR

Regulatory Authorities, Institutional Review Boards/ Independent Ethics Committees (IRBs/IECs), and Principal Investigators will be notified of SAEs in accordance with applicable requirements (eg, GCPs, ICH guidelines, national regulations, and local requirements).

Pharmacyclics has a Pharmacovigilance Committee that will review and evaluate accumulating safety data from the entire clinical study database PCI-32765 at appropriate intervals (e.g., quarterly) to identify new safety signals or increased frequency of events. This will include an aggregate review and comparison to the control group of SAEs that were deemed as “not suspected” of being associated with use of the study drug because they were likely to have been manifestations of underlying disease or that commonly occur in the patient population.

8.0 STATISTICAL CONSIDERATIONS

No formal statistical tests of hypotheses will be performed as this is an open-label, long-term extension study. This study will remain open as long as there are active studies of PCI-32765 with subjects who could be eligible for this protocol.

Demographic characteristics, laboratory parameters, concomitant therapy, and AE incidence rates will be summarized using descriptive statistics. PD and deaths will be presented using a listing. Documented responses will be provided in a listing. All subjects who receive at least 1 dose of study drug in study PCYC-1103-CA will be included in the safety and efficacy analyses. All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Subjects lost to follow-up will be included in statistical analyses to the point of their last evaluation. All study data will be examined using standard data management operating procedures.

9.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Pharmacyclics retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity (e.g., <12 subjects enrolled within 12 months of starting the study)

- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study drug

9.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, IB, and any other relevant supporting information (e.g., all advertising materials or materials given to the subject during the study) to the appropriate IRB/IEC for review and approval before study initiation. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

The investigator is responsible for providing the IRB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB/IEC letter that grants formal approval; and (2) a copy of the IRB/IEC-approved ICF.

9.2 INFORMED CONSENT

The informed consent form (ICF) and process must comply with the United States regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate.

The investigator, or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, the study procedures, anticipated benefits, potential risks, the possible adverse effects, and any discomfort participation in the study may entail. Each subject must provide a signed and dated informed consent before any study-related (nonstandard of care) activities are performed (such as screening). The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

9.3 PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to [Section 9.2](#)), either as part of the informed consent form or as a separate signed document (for example, in the US, a site-specific Health Insurance Portability and Accountability Act [HIPAA] consent may be used). The investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/IECs. As the study sponsor, Pharmacyclics will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

9.4 SUBJECT SCREENING LOG

The investigator must keep a record that lists all subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

9.5 SOURCE DOCUMENTATION REQUIREMENTS

The investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Source documentation for this study will include, but not be limited to, worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, pharmacy records, drug accountability records, and medical consultations (as applicable).

9.6 CASE REPORT FORMS

Electronic case report forms will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physicians' notes, nurses' notes,

clinic charts and other study-specific source documents). Authorized study site personnel (i.e., listed on the Delegation of Authority form) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed in a timely manner. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical data.

The eCRFs exist within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing electronic signature within the EDC system. After database lock, the investigator will receive a copy of the subject data (e.g., paper, CD-ROM or other appropriate media) for archiving at the study site.

9.7 STUDY MONITORING REQUIREMENTS

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Pharmacyclics, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

9.8 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

PCI-32765 must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply PCI-32765 to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

PCI-32765 accountability records must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

Each shipment of PCI-32765 will contain a Clinical Supplies Shipping Receipt form (CSSR) that must be appended to the site's drug accountability records. Additionally a Drug Re-order Form for requesting more PCI-32765 is provided in the pharmacy binder. If it is used, the Drug Re-order Form must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of PCI-32765. Then the designated recipient completes and signs the CSSR. A copy of the signed CSSR must be faxed or mailed to Pharmacyclics at the fax number/ mailing address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (PCYC-1103-CA)
2. subject identification number
3. lot number(s) of PCI-32765 dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/ destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

9.9 FINANCIAL DISCLOSURE

A separate financial agreement will be made between each principal investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each investigator and sub-investigator (as designated on the form FDA 1572) will provide a signed Financial Disclosure Form in accordance with § 21 CFR 54. Each investigator will notify Pharmacyclics or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

9.10 AVAILABILITY AND RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/IEC approval letters (dated), signed form FDA 1572 and Financial Disclosure, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections; SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values; decoding procedures for blinded studies; curricula vitae for study staff, all relevant correspondence and other documents pertaining to the conduct of the study.

Subject identity information will be maintained for 15 years. All other essential documentation will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

9.11 PROTOCOL AMENDMENTS

Pharmacyclics will initiate any other change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/IEC approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign any revised ICF confirming willingness to remain in the study.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the investigator and Pharmacyclics.

9.12 PUBLICATION OF STUDY RESULTS

Pharmacyclics may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the principal investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The medical monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics.

9.13 LIABILITY AND CLINICAL STUDY INSURANCE

In the event of a side effect or injury, appropriate medical care as determined by the investigator/designee will be provided.

If a bodily injury is sustained, resulting directly from the use of the study drug, Pharmacyclics will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the investigator/study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical study insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

10.0 REFERENCES

1. Satterthwaite AB, Witte O. The role of Bruton's tyrosine kinase in B-cell development and function: a genetic perspective. *Immunological Reviews* 2000;175:120-127.
2. Küppers R. Mechanisms of B cell lymphoma pathogenesis. *Nature Reviews Cancer* 2005; 5:251-262.
3. Meeker T, Lowder J, Cleary ML, et al. Emergence of idiotype variants during treatment of B-cell lymphoma with anti-idiotype antibodies. *New England Journal of Medicine* 1985;312:1658-1665.
4. Gururajan M, Jennings CD, Bondada S. Cutting edge: Constitutive B cell receptor signaling is critical for basal growth of B lymphoma. *Journal of Immunology* 2006;176: 5715-5719.
5. Chen L, Monti S, Juszczynski P, et al. SYK-dependent tonic B-cell receptor signaling is a rational treatment target in diffuse large B-cell lymphoma. *Blood* 2008;111:2230-2237.
6. Irish JM, Czerwinski DK, Nolan GP, Levy R. Altered B-cell receptor signaling kinetics distinguish human follicular lymphoma B cells from tumor-infiltrating nonmalignant B cells. *Blood* 2006;108:3135-3142.
7. Robertson MJ, Kahl BS, Vose JM, et al. Phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B-cell lymphoma. *Journal of Clinical Oncology* 2007;25:1741-1746.
8. Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. *ChemMedChem* 2007;2:58-61.
9. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008;111:5446-5456.
10. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology* 2007;25:579-586.
11. Kimby E, Treon SP, Anagnostopoulos A, et al. Update on recommendations for assessing response from the Third International Workshop on Waldenstrom's Macroglobulinemia. *Clin Lymphoma Myeloma* 2006;5:380-383.
12. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, editor. *Evaluation of chemotherapeutic agents*. New York: Columbia University Press; 1949. p 196.
13. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 1982;5:649-655.
14. International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A). March 1995.
15. Food and Drug Administration (FDA). Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (Draft Guidance). September 2010.

16. Smith, TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence based clinical practice guideline. *J of Clinical Oncology* 2006;24:3187-3205.
17. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). <http://medicine.iupui.edu/clinpharm/ddis/table.aspx> Accessed 19 September 2011.
18. Bishop GA, et al. Antigen-specific B-lymphocyte activation. *Crit Rev Immunol* 2003; 23:165–197.
19. Shaffer AL, Rosenwald A, Staudt LM. Lymphoid malignancies: The dark side of B cell differentiation. *Nat Rev Immunol* 2002;2:920–932.
20. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood* 2011; 117:6287-6296.
21. Stevenson FK, Krysov S, Davies AJ, et al. B-cell receptor signaling in chronic lymphocytic leukemia. *Blood* 2011;118: 4313–4320.
22. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension*. Philadelphia:Saunders. 1964. pp. 50-64.
23. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. . Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg.* 1973;60:646-9.

11.0 APPENDICES

Appendix 1. Performance Status Scores

%	Karnofsky Performance Status¹²	Status	Eastern Cooperative Oncology Group (ECOG) Performance Status¹³
100 90	Normal; no complaints; no evidence of disease. Able to carry on normal activity; minor signs or symptoms of disease.	0	Fully active, able to carry on all predisease performance without restriction.
80 70	Normal activity with effort; some signs or symptoms of disease. Care for self. Unable to carry on normal activity or do active work.	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
60 50	Requires occasional assistance but is able to care for most of his or her needs. Requires considerable assistance and frequent medical care.	2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
40 30	Disabled, requires special care and assistance. Severely disabled; hospitalization is indicated though death not imminent.	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
20 10	Hospitalization necessary; very sick; active supportive treatment necessary. Moribund; fatal processes progressing rapidly.	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
0	Dead.	5	Dead.

Appendix 2. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>¹⁷.

The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below: Refer to [Section 5.6.1](#) on instructions for concomitant use of CYP3A inhibitors and inducers with PCI-32765.

Inhibitors of CYP3A	Inducers of CYP3A
<p><u>Strong inhibitors:</u> INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR SUBOXONE TELITHROMYCIN <u>Moderate inhibitors:</u> Aprepitant Erythromycin diltiazem Fluconazole grapefruit juice Seville orange juice Verapamil <u>Weak inhibitors:</u> Cimetidine <u>All other inhibitors:</u> Amiodarone NOT azithromycin Chloramphenicol Boceprevir Ciprofloxacin Delaviridine diethyl-dithiocarbamate Fluvoxamine Gestodene Imatinib Mibefradil Mifepristone Norfloxacin Norfluoxetine star fruit Telaprevir Voriconazole</p>	<p>Carbamazepine Efavirenz Nevirapine Barbiturates Glucocorticoids Modafinil Oxcarbazepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John’s Wort Troglitazone</p>

Source: <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>¹⁷

Appendix 3. Schedule of Assessments

	Screening ^a	Treatment Phase		Follow-up Phase	
		Safety and Efficacy Every 3 Cycles (84 days) ±7 days	Safety Follow-up Prior to anticancer tx or 30 (±7) days after last dose	Post-treatment Follow-up every 3 cycles (84 days) ±7 days until PD ^b	Post-PD Follow-up every 3 months (±7 days)
Informed consent	X				
Confirm eligibility	X				
Medical history	X				
PE ^c /Vital signs ^d /Weight ^d	X	X	X		
Eye-related symptoms	X	X	X		
ECOG status		X	X		
Lab assessments:					
Urine pregnancy test ^e	X		X		
Hematology ^f	X	X	X		
Serum chemistry ^g	X	X	X		
Pharmacodynamics & Pharmacokinetics ^l		Will only be collected when a subject progresses			
Predictive biomarkers & mechanisms of resistance		Approximately once per year			
ECG		If clinically indicated (eg, subjects with palpitations, lightheadedness)			
Dispense study drug ^h		X			
Study drug compliance		X			
Disease assessment ⁱ		X		X	
Concomitant medications ^j	X	X	X		
New anti-cancer treatment ^m			X	X	X
Adverse events ^k	X	X	X		
Survival					X

- a. Screening tests should be performed within 14 days before the first administration of study drug, unless otherwise indicated.
- b. Subjects who did not progress on treatment, but discontinued study drug will be followed every 3 cycles for disease progression.
- c. The screening PE will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Symptom-directed physical examinations will be performed thereafter.
- d. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed. Screening vital signs and weight do not need to be repeated if performed during a prior PCI-32765 protocol within 14 days before the first administration of study drug during the current protocol.
- e. Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
- f. Hematology includes complete blood count with differential and platelet count. Screening hematology does not need to be repeated if performed on prior PCI-32765 protocol within 14 days before the first administration of study drug on this protocol. Subjects who roll into PCYC-1103-CA Study with < 12 months of study drug exposure will need to have hematology performed every 30 days (±7 days) till completion of 12 months on study drug and then hematology will be extended to every 3 cycles (±7 days) while on study treatment.
- g. Serum chemistry includes glucose, calcium, albumin, total protein, sodium, potassium, CO₂, chloride, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, ALT, AST, and total bilirubin. Screening chemistry does not need to be repeated if performed on prior PCI-32765 protocol within 14 days before the first administration of study drug on this protocol. Serum chemistry will be performed every 3 cycles while on study treatment.
- h. One cycle is once daily administration for 28 days. Dispense sufficient study drug until the next scheduled visit.
- i. Objective response will be categorized as complete response (CR), partial response (PR), stable disease, or progressive disease based on the guidelines of each histology (refer to [Appendix 4](#), [Appendix 5](#) and [Appendix 6](#)). The response assessments will be performed once every 3 cycles during the Treatment Phase. All responses must be maintained for at least 2 months to be considered confirmed. Complete responses (CRs) must be confirmed by bone marrow biopsy/aspirate. Progressive disease (PD) must be confirmed by CT. To facilitate lymph node, liver, and spleen assessments in subjects, obtain a CT scan of the chest, abdomen, and pelvis, every 3 cycles for the first 18 cycles from the subject's first dose of study drug in the parent study, then every 6 cycles up to cycle 36, then every 12 cycles (annually) thereafter.
- j. Verify concomitant medication use to ensure subjects' eligibility to remain on study. Record concomitant medications at screening visit and when associated with protocol specified AEs and with SAEs.
- k. Grade 3 and 4 AEs as well as all SAEs, exceptions (refer to [Section 7.1.1](#)) and events of special interest to be collected (refer to [Section 7.2.4](#))
- l. Pharmacodynamic and Pharmacokinetic samples to be collected at the visit when it is determined that the subject has PD.
- m. Once a subject has progressive disease and discontinues study treatment, attempts to collect subsequent anti-cancer therapy should be performed approximately once every 3 months

Appendix 4. Response Assessment Criteria for Chronic Lymphocytic Leukemia (Hallek)⁹

Response	Peripheral Blood ^f	Bone Marrow	Nodes, Liver, and Spleen ^{a,e}
CR	Lymphocytes < 4 x 10 ⁹ /L ANC > 1.5 x 10 ⁹ /L ^b Platelets > 100 x 10 ⁹ /L ^b Hemoglobin > 11.0 g/dL (untransfused) ^b	Normocellular < 30% lymphocytes No B-lymphoid nodules ^d	Normal (e.g., no lymph nodes > 1.5 cm)
CRi	Lymphocytes < 4 x 10 ⁹ /L Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity	Hypocellular < 30% lymphocytes	Normal (e.g., no lymph nodes > 1.5 cm)
PR	Lymphocytes ≥ 50% decrease from baseline or ALC < 4 x 10 ⁹ /L AND ANC > 1.5 x 10 ⁹ /L Or Platelets > 100 x 10 ⁹ /L or 50% improvement over baseline ^b Or Hemoglobin > 11.0 g/dL or 50% improvement over baseline (untransfused) ^b	Not required	≥ 50% reduction in lymphadenopathy ^c and/or in spleen or liver enlargement
PR with lymphocytosis	Subjects who achieved a PR by IWCLL 2008 criteria in all parameters except lymphocyte count will be considered PR with lymphocytosis. Subjects with a PR with lymphocytosis will not be considered to have achieved a PR until there is a 50% reduction in ALC from baseline was achieved or ALC < 4 x 10 ⁹ /L		
SD	Failure to attain CR/PR or progressive disease	Not required	No significant increase or decrease

ANC = absolute neutrophil count; CR = complete remission;
 CRi = CR with incomplete blood count recovery; PR = partial remission

- Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation
- Without need for exogenous growth factors
- In the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes
- Subjects meeting all criteria for a CR with B-lymphocyte nodules on bone marrow exam will be considered nodular partial response (nPR).
- The investigator will assess response in subjects with limited tumor burden at baseline using only the parameters that were abnormal at baseline.
- If all hematological parameters were normal at baseline (eg, Hbg > 11 g/dL, Plt > 100 x 10⁹/L, ANC > 1.5 x 10⁹/L), they must remain normal for the subjects to be considered to have achieved a response.

Progressive disease for CLL is characterized by ≥ 1 of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (> 1.5 cm), de novo appearance of hepatomegaly or splenomegaly, or other organ infiltrates
- An increase of $\geq 50\%$
- in longest diameter of any previous site
- in the previously noted enlargement of the liver or spleen
- in blood lymphocytes with $\geq 5 \times 10^9/L$ B cells only in setting of enlarging lymph node, liver, or spleen (note: isolated elevation of WBC by itself will not be considered progressive disease unless subject becomes symptomatic from this)

Appendix 5. Response Assessment Criteria for Lymphoma (Cheson 2007)¹⁰

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or progressive disease	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET (b) Variably FDG avid or PET negative; no change in size of previous lesions on CT		

Abbreviations: CR = complete response, CT = computed tomography, FDG = [¹⁸F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

Progressive disease for Non-Hodgkin’s lymphoma is characterized by any new lesion or increase by ≥ 50% of previously involved sites from nadir for example:

- Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of > 1 node, or ≥ 50% increase in longest diameter of a previously identified node >1 cm in short axis
- Lesions PET positive if FDG-avid lymphoma or PET positive before therapy
- > 50% increase from nadir in the SPD of any previous lesions in the liver or spleen
- New or recurrent involvement in the bone marrow

An increase of ≥ 50% in blood lymphocytes with ≥ 5 x 10⁹/L B cells only in setting of enlarging lymph node, liver, or spleen (note: isolated elevation of WBC by itself will not be considered progressive disease unless subject becomes symptomatic from this)

Appendix 6. Response Assessment Criteria for Waldenström's Macroglobulinemia (Kimby 2006)¹¹

Response	Definition
CR	A disappearance of serum and urine monoclonal protein determined by immunofixation, absence of malignant cells in bone marrow determined by histologic evaluation, resolution of adenopathy/organomegaly, (confirmed by computed tomography [CT] scan), and no signs or symptoms attributable to WM. Recommendation of the CR status is required ≥ 6 weeks later with a second immunofixation.
PR	A $\geq 50\%$ reduction of serum monoclonal IgM concentration determined by protein electrophoresis, $\geq 50\%$ decrease in adenopathy/organomegaly on physical examination or on CT scan, and no new symptoms or signs of other active disease.
SD	A $< 25\%$ reduction and $< 25\%$ increase of serum monoclonal IgM determined by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms caused by disease and/or signs of WM.
PD	A $\geq 25\%$ increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinical significant findings caused by disease (eg, anemia, thrombocytopenia, leukopenia, or bulky adenopathy/organomegaly) or symptoms (eg, unexplained recurrent fever $\geq 38.4^{\circ}\text{C}$, drenching night sweats, $\geq 10\%$ weight loss, hyperviscosity, neuropathy, or symptomatic cryoglobulinemia) attributable to WM.

Abbreviations: WM=Waldenström's Macroglobulinemia, CR = complete response, CT = computed tomography, PR = partial response, SD = stable disease, PD=progressive disease

Appendix 7. Child-Pugh Score^{22,23}

Measure	1 point	2 points	3 points
Total bilirubin, $\mu\text{mol/L}$ (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C